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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,734	10/31/2003	Denise L. Faustman	00786/405003	3056

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
01/24/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/698,734	FAUSTMAN, DENISE L.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,30,45,46 and 53-62* is/are pending in the application.

4a) Of the above claim(s) *58,61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 30, 45, 46, 53-57,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/30/07 is acknowledged.

Claims 1-12, 30,45,46, 53-62 are pending.

Claims 58, 61 and 62 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-12, 30, 45, 46, 53-57,59 and 60 read on a method for increasing or maintaining the number of functional cells of a predetermined type in an organ or tissue of mammal, comprising administering to said mammal a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances are under consideration in the instant application.

In view of the amendment, filed 10/30/07 the following rejections remain

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-12, 30, 45, 46, 53-57 , 59 and 60 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of restoration of normoglycemia or to treat salivary gland defects or to gain hearing function in NOD mice , comprising administering Hox-11 expressing splenocytes alone or in combination with administering TNF-α or TNF-α agonist does not reasonably provide **enablement** for a method for increasing or maintaining the number of functional cells of predetermined type of any organ or tissue in any mammal said method comprising administering Hox-11 expressing splenocytes alone or in combination with administering TNF-α or TNF-α agonist claimed in claims 1-12, 30, 45, 46, 53-57 , 59 and 60. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action 03/12/07.

Applicant's arguments, filed 10/30/07 have been fully considered, but have not been found convincing.

Applicant assert that : (i) the present specification exemplifies the invention by reference to preferred embodiment which examines the restoration of beta-islet cells following administering of Hox-11 expressing splenocytes using NOD mouse model; (ii) As further evidence for the full scope of the enablement of the instant claims the enclosed Declaration by Dr . Faustman indicated that administering of Hox-11 expressing splenocytes into NOD mouse results in treating salivary gland defects and gain hearing function .

Contrary to Applicant's assertion as has been discussed in the previous Office Action the specification only discloses limited data obtained on NOD female mice wherein treatment with live splenocytes and CFA prolong survival of syngeneic islet graft and restoration of normoglycemia (see examples 1-4 and Table 1 and 2 in particular). Example 8 in the instant Specification is a prophetic examples that indicate what the inventor thinks might happen in the experiments which have not actually been performed. The date presented in the declaration by Dr. Faustman provided additional data obtained in NOD mouse. It is noted that the Examiner acknowledge that the instant claims are enabled for a method of restoration of normoglycemia or to treat salivary gland defects or to gain hearing function in NOD mice.

However, the specification does not adequately teach how to effectively increasing or maintaining the number of any functional cells of any predetermined type in any organ or any tissue of any mammal, including human comprising administering to said mammal a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances, as claimed in the instant claims.

Moreover, it is noted that in the disclosed examples the specification as well as additional data provided in declaration of Dr. Faustman are relying on the data obtained in NOD mouse model that applicant believes correlates well with human therapy.

However, Atkinson et al. .,(Nature, 1999, V.5, pages 601-604) teach that in addition to certain NOD strain-specific characteristics that distinguish these mice from humans at risk for type I diabetes important genus-specific features distinguish the murine diabetes as well, such as resistance to ketoacidosis or the absence of the murine homolog of HLA-DR molecules on APC. Investigators have not always considered that. Unfortunately, in a genetically heterogeneous human population containing individuals at high risk of type I diabetes development, there is little evidence that many of them would have a comparable set of immune deficiencies that prove as malleable. In NOD mice, type 1 diabetes development is well-choreographed. In contrast, the natural history of type 1 diabetes in human is such that the age of disease onset is extremely broad; symptoms occur at any time from the first years of life to well beyond 50 years of age. It is clear that the genus-unique and strain-specific aspects of diabetes in NOD mice must be fully understand and appreciated if we are to know which therapeutic protocols are reasonable to

extrapolate to humans and which are not. Exploitation of the NOD genome for clinical research is yet to be done (see pages 602, 603 and 604 in particular).

It is noted that the Specification explicitly stated that even restoration of near normal pancreatic islet histology was observed only in diabetic NOD mice treated with CFA and received β2 $M^{-/-}$ allograft. Pancreatic islets were not detected in any diabetic NOD mice treated with CFA and syngeneic NOD islets. Kaufman et al., (J of Immunol. 1997, V.158, pages 2435-2442) teach that NOD mouse have been characterized to have a number of abnormalities in hematolymphopoiesis. The proportion of donor chimerism in NOD mice that initially repopulated as mixed chimeras tended to increase significantly over time to become predoninatly donor (see page 2438 in particular). Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Feldman et al . further teach that in a chronic immune-driven inflammatory response there are a number of pathways that become engaged and effective therapy in immune inflammatory diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway. Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans. Similarly, Couzin (Science, 2006, V.311, page 1694) teaches that recent studies attribute that reversal to a therapy that's **too toxic for humans** although it has previously been used to prevent and occasionally treat mouse diabetes.

Moreover, an effective protocol for a method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue in any mammal including human is subject to a number of factors which enter the picture beyond simply the administration to the subject a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances, as claimed in the instant claims. Demonstrating prolong survival of syngeneic islet graft restoration of normoglycemia in diabetic NOD mice or treating salivary gland defects or to gaining hearing function in NOD mice after administering live splenocytes and CFA cannot alone support the predictability of a method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue, by simply administering to a mammal a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances. Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect immune response such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to enhance an immune response will vary depending upon factors such as the condition of the host and burden of disease.

Also an issue is that applicant still has not addressed how this method of treatment would be effective in view of the substantial art teachings pro-inflammatory effects of TNF-α on other cells involved in autoimmune disease. For example, Corbett et al. (Proc Natl Acad Sci U S A. 1993 Mar 1 ;90(5): 1731-5) teaches that in human cells TNF-α potentiates the IL-1 + IFN-γ induced production of nitric oxide, a molecule which participates in the beta-cell dysfunction associated with insulin-dependent diabetes mellitus (see entire document, in particular Abstract and pages 1731-1732). Likewise, Altomonte et al. (Clin. Rheumatol. 1992 Jun;11 (2):202-5) teaches that TNF-α can induce the production of IL-1b, and that both molecules can act locally to induce bone and cartilage resorption, synoviocyte proliferation and the production of prostaglandins and proteases that amplify the destructive process in the joint (see, for example, Introduction, in particular page 202) - certainly not something one would want to do in a rheumatoid arthritis patient or a lupus patient who often has overlapping symptoms with the RA patient. Furthermore, as taught by Feldman et al. (Transplant Proc. 1998 Dec;30(8):41267, TNF-α is involved in the expression of various adhesion molecules responsible for recruiting leucocytes to inflammatory sites (see, in particular, page 4126, right column, 1st paragraph).

Thus, since there is no animal model studies and data in the specification to show the effectively of the claimed method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue in any mammal including human comprising administration to the subject a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances, and the art recognized possible toxic or/and side effects for human of substances that has previously been used to prevent and occasionally treat mouse diabetes it is unpredictable how one skilled in the art can practice the invention without an undue amount of experimentation. Therefore, it is not clear that the skilled artisan could predict the efficacy of a claimed method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue in any mammals including human.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue comprising administration to the subject a composition of enriched pluripotent cells that express the Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-12, 30, 45, 46, 53-57 59 and 60 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 and 35-49 of co-pending Application NO:10/358,664. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-14 and 35- 49 of co-pending Application NO:10/358,664 recites a method of increasing or maintaining the number of functional cells of a predetermined type in a mammal, comprising administering pluripotent cells and TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1-12, 30, 45, 46, 53-57 59 and 60 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6660487 or claims 1-18 of US Patent 6,599,710 . Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-15 of U.S. Patent

No. 6660487 or claims 1-18 of US Patent 6,599,710 recites a method of increasing or maintaining the number of functional cells of a predetermined type in a mammal, comprising administering pluripotent cells and TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances.

It is noted that Applicant indicated that when the instant claims are found to be otherwise allowable, Applicant will address these rejection.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571/ 272-0878.
The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PRIMARY EXAMINER
1/18/08